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Published in:
eJournal of Oral And Maxillofacial Research

DOI (link to publication from Publisher):
10.5037/jomr.2020.11203

Publication date:
2020

Document Version
Publisher's PDF, also known as Version of record

Short-term Haematological Parameters Following Surgical Removal of Mandibular Third Molars with Different Doses of Methylprednisolone Compared with Placebo. A Randomized Controlled Trial

Marie Kjærgaard Larsen[1], Thomas Kofod[2], Kirsten Duch[3], Thomas Starch-Jensen[1]

[1]Department of Oral and Maxillofacial Surgery, Aalborg University Hospital, Denmark.
[2]Department of Oral and Maxillofacial Surgery, Rigshospitalet, Copenhagen University Hospital, Denmark.
[3]Clinical unit of Biostatistics, Aalborg University Hospital, Aalborg, Denmark.

Corresponding Author:
Marie Kjærgaard Larsen
Department of Oral and Maxillofacial Surgery
Aalborg University Hospital
18-22 Hobrovej, DK-9000 Aalborg
Denmark
Phone: +45 97 66 27 95
Fax: +45 97 66 28 25
E-mail: marie.kjaergaard@rn.dk

ABSTRACT

Objectives: To evaluate the influence of a single intraoperative injection of methylprednisolone on short-term haematological parameters following surgical removal of mandibular third molars.
Material and Methods: Fifty-two patients with indications for surgical removal of bilateral impacted mandibular third molars were included in a randomized, split-mouth and double-blinded study design. Each molar were randomly allocated into one of following four groups: 20 mg methylprednisolone, 30 mg methylprednisolone, 40 mg methylprednisolone and placebo. Peripheral blood samples were obtained before and three days after surgery. Haematological parameters involving haemoglobin, white blood cell count and C-reactive protein (CRP) were evaluated and expressed as mean changes. Level of significance was 0.05. Furthermore, outcomes were correlated for age, sex, smoking and time of surgery.
Results: There were no significant differences in postoperative haematological parameters with different doses of methylprednisolone compared with placebo. Peripheral blood samples revealed decreased level of haemoglobin and increased level of leucocytes and CRP in each group. Smokers displayed a significant lower level of haemoglobin and CRP compared with non-smokers ($P < 0.05$) and level of eosinophils decreased significantly with increasing age ($P < 0.05$).
Conclusions: This study indicates that a single intraoperative injection of methylprednisolone seems not to cause suppression of short-term haematological parameters compared with placebo following surgical removal of mandibular third molars.

Keywords: corticosteroids; C-reactive protein; leucocytes; mandible; methylprednisolone; third molar.

Accepted for publication: 11 June 2020
To cite this article:
Larsen MK, Kofod T, Kirsten D, Starch-Jensen T.
Short-term Haematological Parameters Following Surgical Removal of Mandibular Third Molars with Different Doses of Methylprednisolone Compared with Placebo. A Randomized Controlled Trial
J Oral Maxillofac Res 2020;11(2):e3
URL: http://www.ejomr.org/JOMR/archives/2020/2/e3/v11n2e3.pdf
doi: 10.5037/jomr.2020.11203

INTRODUCTION

Surgical removal of mandibular third molars (M3s) is a common surgical procedure in dentistry and oral and maxillofacial surgery. Facial swelling, pain and trismus are well-known sequelae caused by an inflammatory response to the surgical trauma [1,2]. Prophylactic measures including pharmacological therapies, cryotherapy, local compression and surgical drains are frequently used to diminish the inflammatory response following surgical removal of M3 [3-7]. Corticosteroids are synthetic analogues of natural steroid hormones produced by the adrenal cortex and have potent anti-inflammatory properties [8,9]. The clinical efficacy of synthetic corticosteroids to diminish postoperative sequelae following surgical removal of M3 have previously been assessed in systematic reviews and meta-analyses [10-13].

Systemic or local administration of corticosteroids interact with biochemical and haematological parameters including haemoglobin, white blood cell counts and C-reactive protein (CRP) [14-17]. Level of haemoglobin in peripheral blood is increased after administration of corticosteroid, possibly by retarding erythrophagocytosis [16]. Level of leucocytes is also increased after administration of corticosteroids due to increase rate of entrance from bone marrow and decrease rate of removal from the vascular compartment [18], whereas diminished level of lymphocytes, eosinophils, monocytes and basophils have been reported after administration of corticosteroids [18,19]. Level of CRP after tissue injury or inflammation is decreased after corticosteroid therapy due to diminish formation of cytokines [17,20]. It has been reported that the influence of corticosteroids on biochemical and haematological parameters depends on administration route, dosages and therapy duration [19]. A previous study estimated number of peripheral eosinophils after perioral administration of preoperative corticosteroids following surgical removal of M3 [21]. Facial swelling was statistically significant diminished after administration of hydrocortisone and a 50% reduction in the level of eosinophils compared with placebo. However, assessment of haematological parameters after systemic or local administration of corticosteroids following surgical removal of M3 has never previously been assessed. Therefore, the purpose of this double-blinded randomized controlled trial was to assess the influence of a single intramuscular injection of methylprednisolone on short-term haematological parameters, changes in inflammatory response and possible side effects compared with placebo following surgical removal of mandibular third molars.

MATERIAL AND METHODS

Study design and sample

The study was conducted at the Department of Oral and Maxillofacial Surgery, Aalborg University Hospital, Denmark between March 2018 and January 2019. The study protocol was approved by the Danish Health and Medicines Authority, Research Ethics Committee and Danish Data Protection Agency (approval no. N-20170016). The study was performed in accordance with Good Clinical Practice (GCP), Declaration of Helsinki II and Consolidated Standards of Reporting Trials (CONSORT) statement [22]. Patients were recruited by public invitation through Facebook, personal contacts or scheduled for surgical removal of M3 due orthognathic treatment of a facial deformity. Oral and written information regarding the study was provided prior to enrolment, and written informed consent was obtained from all included patients. Participation was voluntary, and patients could at any given time withdraw from the study.

Sample size calculation

Sample size was calculated using Clincalc.com (http://clincalc.com/stats/samplesize.aspx) to ensure adequate power for the study including a difference of 20 mm in VAS score on the first postoperative day. Analysis revealed that 16 patients per group would be necessary to provide 80% power with an alpha value of 0.05. Sample size was increased to 26 M3 in each group to compensate for possible dropouts.

Study population

Patients scheduled for surgical removal of bilateral impacted M3 were included. Position of M3 was assessed on panoramic radiograph and classified using Pell and Gregory system and Winters classification [23]. Inclusion and exclusion criteria are outlined in Table 1.

Randomization and blinding

A computer-aided randomization was used to allocate each M3 cases into four groups. A randomization scheme was fabricated including an allocation number for each M3. The pharmacy at Aalborg University Hospital, Aalborg, Denmark, preserved the randomization scheme until the study was unblinded. An assistant nurse received an e-mail with

Table 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
- Bilateral symmetrical impacted mandibular third molars. - Indication for removal of mandibular third molars. - Age between 18 and 40 years.	- Acute infection in the oral cavity at the time of surgery. - Previous maxillofacial trauma. - Craniofacial clefts or syndromes. - Systemic bone disease (i.e. arthritis) or diabetes mellitus. - Active acne vulgaris, viral and fungal infections. - Psychological disease. - Medication as bisphosphonate, anticoagulants and other drugs that have an influence on corticosteroids. - Pregnancy and breastfeeding. - Failure to attend follow-up. - Known allergy to methylprednisolone and other inactive ingredients.

the randomization numbers and allocated each M3 case into one of the following four groups:

- Group I: placebo (isotonic saline solution);
- Group II: 20 mg methylprednisolone;
- Group III: 30 mg methylprednisolone;
- Group IV: 40 mg methylprednisolone.

Patients, surgeon, dental assistant as well as assessor were not informed about the allocation group. A trained assistant nurse fabricated syringes containing either placebo or methylprednisolone. All syringes contained 1.05 mL of mixtures. Syringes containing methylprednisolone were mixed with isotonic saline solution. The colour of the mixtures was identical. Thus, each syringe from the four groups had similar appearance and quantity.

Haematological parameters

Blood samples were obtained by a medical laboratory technologist at Aalborg University Hospital, Denmark. Blood samples were collected from each patient before (T0) and three days (T1) after surgical removal of M3 with no regard to time of the day, physical activity or fasting. Data were registered and stored in the patients' case report file. A total of 8 mL of whole blood was collected from the cubital vein. Complete haemogram test of the blood samples was conducted within two hours by Sysmex XN-9000 haematology analyzer (Sysmex Europe GmbH; Norderstedt, Germany) and Cobas 8000 (Roche Diagnostics International Ltd; Rotkreuz, Switzerland). Level of haemoglobin (mmol/L), leucocytes (counts x 10^9/L), neutrophils (counts x 10^9/L), eosinophils (counts x 10^9/L) and CRP (counts/L) were analysed.

Surgical procedure

A standardized surgical procedure was performed in all patients by the same trained surgeon (MKL). Patients had one M3 removed at each time. Removal of the contralateral M3 was scheduled, four to six weeks later. All patients received prophylactic analgesic including 400 mg ibuprofen (Ipren® - Takeda Pharma A/S; Hobro, Denmark) and 1,000 mg paracetamol (Pinex®, Actavis Nordic A/S; Søborg, Denmark), one hour prior to surgery.

Surgical removal of M3 was performed under local anaesthesia with 20 mg/mL mepivacaine hydrochloride and 5 µg/mL adrenaline (Carbocain-Adrenalin® - AstraZeneca; Copenhagen, Denmark). Immediately after application of local anaesthesia, an injection of methylprednisolone or placebo was given in the masseter muscle at the ipsilateral site. A mucosal incision was made from the anterior border of the ascending mandibular ramus to the distal part of the second molar continuing marginal to the lower first molar. The mucosal flap was elevated. Facial and distal bone removal around the M3 was performed with a round burr on a straight hand-piece under continuous irrigation with saline. Sectioning of the crown or roots was performed as necessary with a fissure bur and the same hand-piece. Extraction socket and surrounding bone was copiously irrigated with a saline solution, and the mucosal flap was sutured with a resorbable suture (Ethicon Vicryl Rapide™ suture 4-0 - Johnson and Johnson Medical Gmbh; Norderstedt, Germany). A small gauze pack was applied to the surgical site and usual postoperative instructions were given to the patients.

Postoperative medications included 400 mg of ibuprofen three times a day (Ipren®) and 1.000 mg paracetamol (Pinex®) four times a day. Patients were also instructed to mouth rinse three times a day with 0.12% chlorhexidine (Klorhexidin Mundskyl 0.12% - Faaborg Pharma; Faaborg, Denmark).

Statistical analysis

Data management and statistical analysis was performed with Excel, version 2013 (Microsoft; Redmond, Washington, USA) and R, version 3.6.1 (Missouri, USA). Difference in level of haemoglobin,

leucocytes, neutrophils, eosinophils and CRP were analysed with a generalized estimating equation analysis, Generalized Estimating Equation analysis to compensate for the fact that some data were not normal distributed. The results were expressed as mean with a 95% confidence interval (CI). P value less than 0.05 was considered as statistically significant. The analysis was descriptive and adjusted for age, sex, smoking and time of surgery. Parametric data were expressed as mean and standard deviation (M [SD]).
Descriptive analysis of secondary categorical variables including smoking habits, anatomical position of M3 and infection rate was analysed using Fishers exact test, when the number of observations in each category was not unreasonably small.

RESULTS

Study population

The present study included 52 patients (16 men and 36 female) with a mean age of 25.9 (6) years (range from 18 to 39) and surgical removal of 104 M3 (Table 2 and Figure 1). One patient dropped out

Table 2. Baseline characteristics

Variable	Level	Placebo (n = 26)	20 mg (n = 26)	30 mg (n = 26)	40 mg (n = 26)	Total (n = 104)
Sex, N (%)	Male	8 (30.8)	8 (30.8)	8 (30.8)	8 (30.8)	32 (30.8)
	Female	18 (69.2)	18 (69.2)	18 (69.2)	18 (69.2)	72 (69.2)
Age, years	Mean (SD)	24.62 (4.97)	26.81 (6.52)	25.62 (6.17)	26.65 (6.28)	25.92 (5.99)
	Median	24	25.5	23	24	24
	Q1; Q3	21; 26.75	22; 30	21; 29	22.25; 30	21; 29
	Min	18	18	18	18	18
	Max	38	39	39	39	39
Smoking, N (%)	No	24 (92.3)	24 (92.3)	22 (84.6)	24 (92.3)	94 (90.4)
	Yes	2 (7.7)	2 (7.7)	4 (15.4)	2 (7.7)	10 (9.6)

N = number; Q1 = first quartile; Q3 = third quartile; SD = standard deviation.

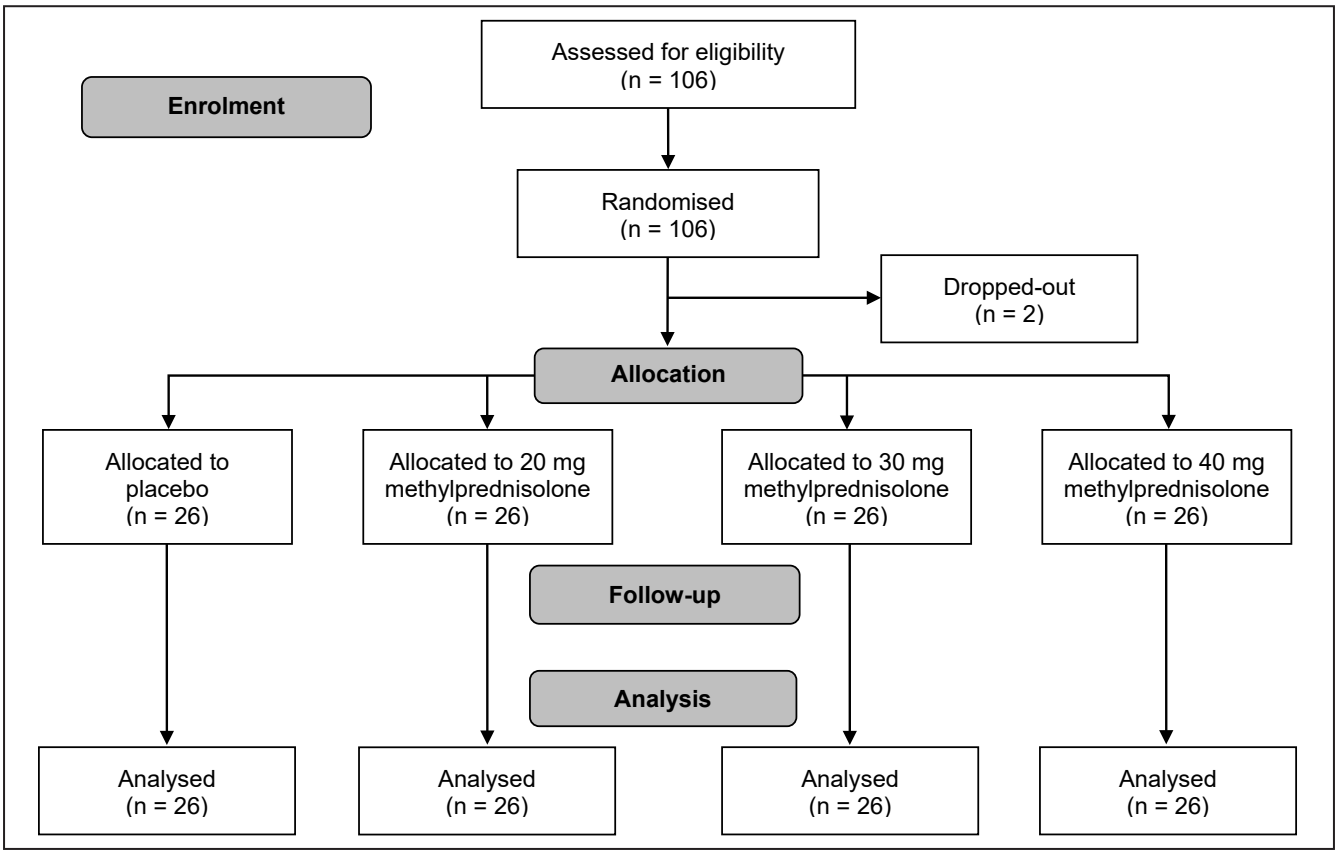

Figure 1. Consort flow diagram.

Table 3. Anatomical position of mandibular third molars and time of surgery

Variable	Level	Placebo (n = 26)	20 mg (n = 26)	30 mg (n = 26)	40 mg (n = 26)	Total (n = 104)
Anatomical position (Winter), N (%)	**1**	10 (38.5)	8 (30.8)	10 (38.5)	5 (19.2)	33 (31.7)
	2	6 (23.1)	8 (30.8)	4 (15.4)	10 (38.5)	28 (26.9)
	3	5 (19.2)	4 (15.4)	8 (30.8)	6 (23.1)	23 (22.1)
	4	5 (19.2)	6 (23.1)	4 (15.4)	5 (19.2)	20 (19.2)
Anatomical position (Pell and Gregory transversal), N (%)	**1**	0 (0)	1 (3.8)	0 (0)	0 (0)	1 (1)
	2	26 (100)	24 (92.3)	26 (100)	26 (100)	102 (98.1)
	3	0 (0)	1 (3.8)	0 (0)	0 (0)	1 (1)
Anatomical position (Pell and Gregory vertical), N (%)	**1**	7 (26.9)	5 (19.2)	9 (34.6)	8 (30.8)	29 (27.9)
	2	18 (69.2)	18 (69.2)	16 (61.5)	16 (61.5)	68 (65.4)
	3	1 (3.8)	3 (11.5)	1 (3.8)	2 (7.7)	7 (6.7)
Time of surgery (minutes)	**Mean (SD)**	9.27 (3.79)	8.77 (3.9)	9.04 (5.87)	11.73 (6.77)	9.7 (5.3)
	Median	9.5	7	6	9.5	8
	Q1; Q3	6; 10	6; 10.75	5.25; 10	8; 15.75	6; 11.25
	Min; max	5; 18	5; 20	4; 30	4; 31	4; 31

N = number; Q1 = first quartile; Q3 = third quartile; SD = standard deviation.

during the inclusion period and was replaced by another patient. No statistically significant differences were found in the demographic as well as clinical and radiographic characteristics among the study groups including gender, age, anatomical classification of the M3 (P = 0.66), smoking (P = 0.836) and time of surgery (P = 0.33) (Table 2 and 3). Mean surgical time was 9.42 (5.18) minutes. Patients underwent surgical removal of one M3, while the other M3 was removed after 58.8 days (range from 8 to 157). The study was unblinded 13th of May 2019.

Postoperative antibiotics involving phenoxymethylpenicillin 800 mg (Primcillin® - Meda A/S; Ballerup, Denmark) four times a day and metronidazole 500 mg (Metronidazol "DAK" - Takeda Pharma A/S; Hobro, Denmark) two times a day for seven days) were prescribed in 22 cases out of 104 (21.1%) due to major swelling, pus or increased body temperature. Distribution of infection among the four groups was equal with no significant difference (P = 0.676). Postoperative bleeding occurred in two cases out of 104 (1.9%). The bleeding was sufficient treated with additional sutures and compression. None of the patients complained of discomfort or complications related to blood samples. No further complications were observed.

Haemoglobin

Mean level of haemoglobin decreased in all groups from 8.79 (0.79) mmol/L (T0) to 8.51 (0.74) mmol/L (T1). There were no significant differences in the level of haemoglobin from T0 to T1 between 20 mg methylprednisolone (P = 0.606), 30 mg methylprednisolone (P = 0.404) or 40 mg methylprednisolone (P = 0.828) compared with placebo (Table 4A and Figure 2). No significant differences in the level of haemoglobin were observed from T0 to T1, when results were adjusted for age (P = 0.573), sex (P = 0.212) and time of surgery (P = 0.616). However, a significant difference in the level of haemoglobin was observed, when the results were adjusted for smoking (P < 0.05) indicating that smokers display a lower level of haemoglobin compared with non-smokers at T0 and T1, respectively.

White blood cell count

Mean level of leucocytes increased in all groups from 6.33 (1.36) 10^9/L (T0) to 7.85 (2.18) 10^9/L (T1). There were no significant differences in the level of leucocytes between 20 mg methylprednisolone (P = 0.449), 30 mg methylprednisolone (P = 0.761) and 40 mg methylprednisolone compared with placebo (P = 0.872) from T0 to T1 (Table 4A and Figure 3). No significant differences in the level of leucocytes were observed from T0 to T1, when results were adjusted for age (P = 0.805), sex (P = 0.814), smoking (P = 0.674) and time of surgery (P = 0.139).

Mean level of neutrophils increased in all groups from 3.44 (1.12) 10^9/L (T0) to 4.88 (1.96) 10^9/L (T1). There were no significant differences in the level of neutrophils between 20 mg methylprednisolone (P = 0.562), 30 mg methylprednisolone (P = 0.454) and 40 mg methylprednisolone compared with placebo (P = 0.555) from T0 to T1 (Table 4B and Figure 4).

Table 4A. Results of blood sampling. The difference between before surgery and three days after surgery

Group	Haemoglobin				Leucocytes			
	Estimate	95% CI	SD	P	Estimate	95% CI	SD	P
0 mg	Reference	-	-	-	-	-	-	-
20 mg	-0.05	-0.22; 0.13	0.088	0.606	0.39	-0.62; 1.4	0.517	0.449
30 mg	0.08	-0.11; 0.28	0.101	0.404	-0.19	-1.42; 1.04	0.629	0.761
40 mg	0.02	-0.15; 0.19	0.087	0.828	0.09	-0.98; 1.16	0.546	0.872

CI = confidence interval; SD = standard deviation.

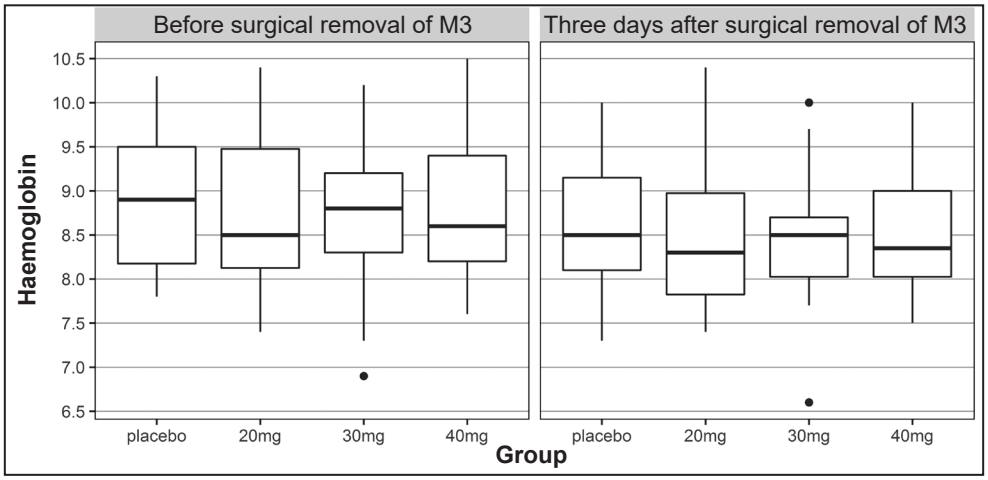

Figure 2. Boxplot of the level of haemoglobin (mmol/L) before and three days after intramuscular administration of methylprednisolone and surgical removal of mandibular third molar (M3).

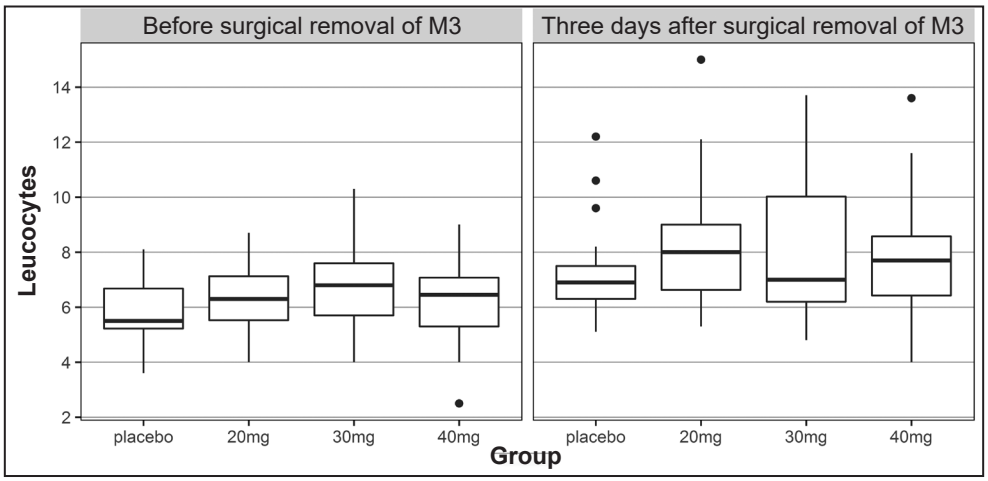

Figure 3. Boxplot of the level of leucocytes (/L) before and three days after intramuscular administration of methylprednisolone and surgical removal of mandibular third molar (M3).

No significant differences in the level of neutrophils were observed from T0 to T1, when results were adjusted for age (P = 0.531), sex (P = 0.563), smoking (P = 0.671) and time of surgery (P = 0.055).

Mean level of eosinophils decreased in all groups from 0.17 (0.11) 10^9/L (T0) to 0.14 (0.08) 10^9/L (T1). There were no significant differences in the level of eosinophils between 20 mg methylprednisolone (P = 0.612), 30 mg methylprednisolone (P = 0.956) and 40 mg methylprednisolone compared with placebo (P = 0.775) from T0 to T1 (Table 4B and Figure 5). No significant differences in level of eosinophils were observed from T0 to T1, when results were adjusted for sex (P = 0.411), smoking (P = 0.061) and time of surgery (P = 0.385). However, a significant difference in the level of eosinophils was seen from T0 to T1, when the results were adjusted for age (P = 0.05) revealing a larger reduction in level of eosinophils at T1 with increasing age.

Table 4B. Results of blood sampling. The difference between before surgery and three days after surgery

Group	Neutrophils				Eosinophils				C-reactive protein			
	Estimate	95% CI	SD	P	Estimate	95% CI	SD	P	Estimate	95% CI	SD	P
0 mg	-	-	-	-	-	-	-	-	-	-	-	-
20 mg	0.27	-0.64; 1.19	0.467	0.562	0.009	-0.03; 0.05	0.019	0.612	-4.78	-17.65; 8.08	6.565	0.466
30 mg	-0.45	-1.61; 0.72	0.594	0.454	-0.001	-0.04; 0.04	0.019	0.956	-10.26	-20.31; -0.2	5.131	< 0.05
40 mg	-0.3	-1.28; 0.68	0.5	0.555	-0.005	-0.04; 0.03	0.019	0.775	-9.92	-22.17; 2.32	6.249	0.112

CI = confidence interval; SD = standard deviation.

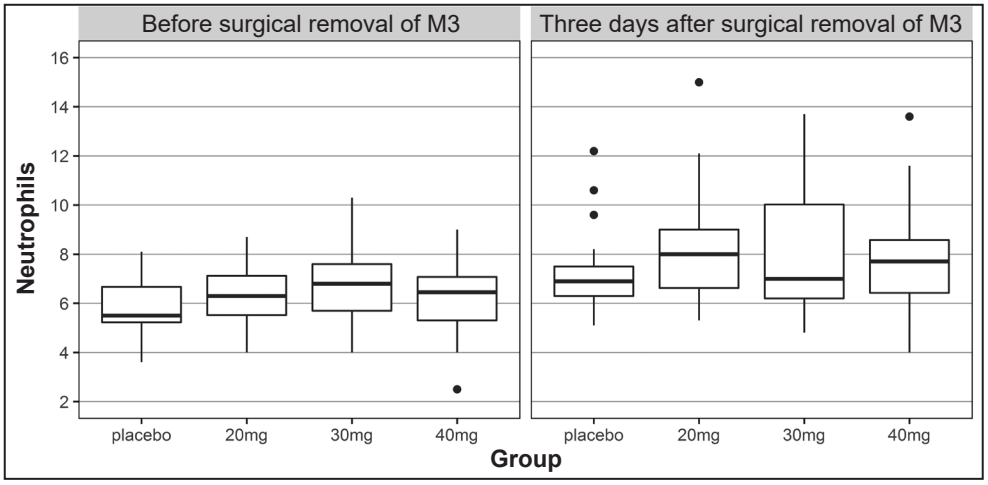

Figure 4. Boxplot of the level of neutrophils ($x10^9$/L) before and three days after intramuscular administration of methylprednisolone and surgical removal of mandibular third molar (M3).

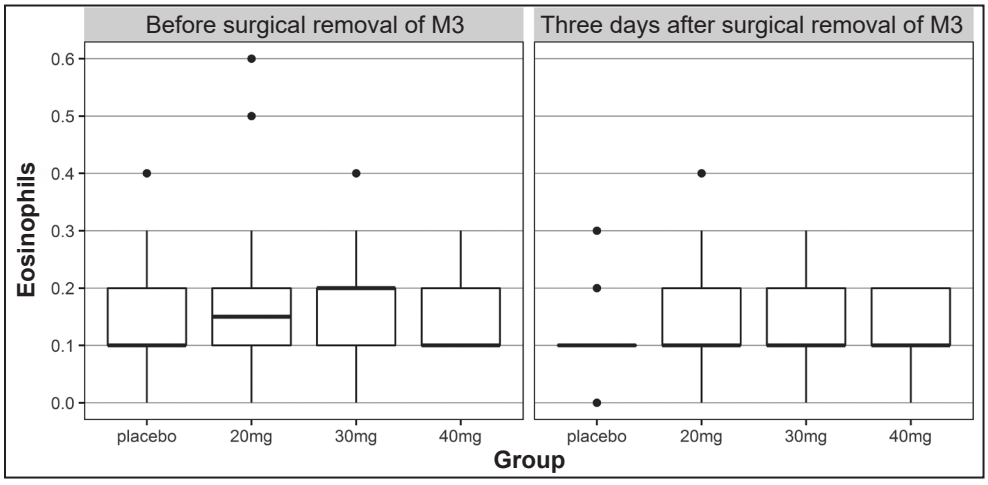

Figure 5. Boxplot of the level of eosinophils ($x10^9$/L) before and three days after intramuscular administration of methylprednisolone and surgical removal of mandibular third molar (M3).

C-reactive protein

Mean level of CRP increased in all groups from 2.36 (2.63)/L (T0) to 14.92 (22.03)/L (T1). There were no significant differences in the level of CRP between 20 mg methylprednisolone (P = 0.466) and 40 mg methylprednisolone (P = 0.112) compared with placebo from T0 to T1. However, mean level of CRP was significantly decreased with 30 mg methylprednisolone compared with placebo (P < 0.05) from T0 and T1 (Table 4B and Figure 6). No significant differences in the level of CRP were observed from T0 to T1, when the results were adjusted for age (P = 0.748), sex (P = 0.83) and time of surgery (P = 0.104). However, a statistically significant difference in the level of CRP was seen between smokers and non-smokers (P < 0.05) at T1 indicating that smokers have a lower increase in the level of CRP compared with non-smokers.

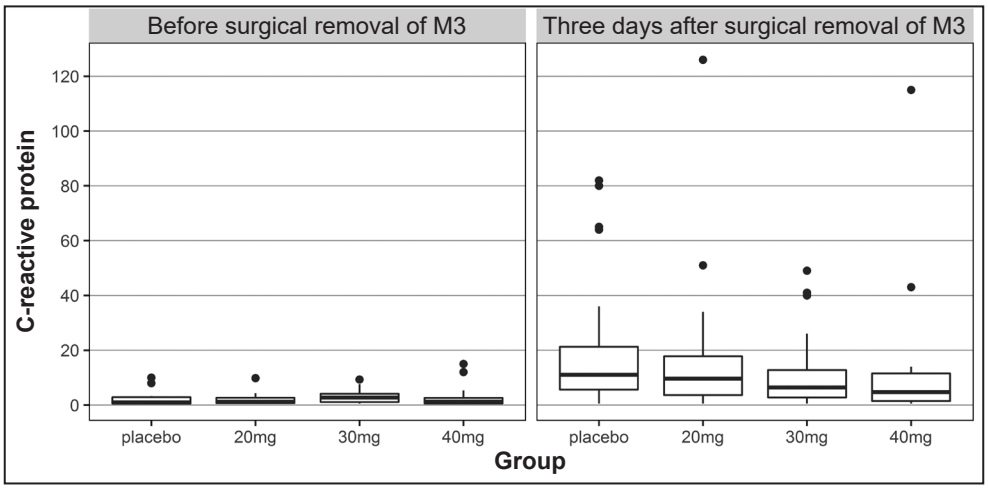

Figure 6. Boxplot of the level of C-reactive protein (mg/L) before and three days after intramuscular administration of methylprednisolone and surgical removal of mandibular third molar (M3).

DISCUSSION

Indication for the use of corticosteroids or other medications to diminish postoperative sequelae following surgical removal of M3 is an important consideration for healthcare professionals. Advantages and disadvantages should always be considered, especially if the drugs interfere or suppress normal body functions. However, haematological parameters, adrenal insufficiency or increased risk of infections following surgical removal of M3 with administration of different doses of corticosteroids have never previously been investigated. The present double-blinded randomized controlled trial demonstrated no significant differences in short-term haematological parameters following surgical removal of M3 with a single intramuscular injection of methylprednisolone compared with placebo. Postoperative peripheral blood samples revealed generally decrease in level of haemoglobin and an increase in level of leucocytes and CRP compared with preoperative blood levels. Subgroup analyses indicated that increased age and smoking influence haematological parameters following surgical removal of M3.

Synthetic corticosteroids display dissimilar pharmacokinetic properties and duration of action [10]. Methylprednisolone was used in the present study since other synthetic corticosteroids are not available in Denmark for intramuscular injection following surgical removal of M3. Methylprednisolone is classified as intermediate duration of action with plasma half-life time of 3 to 4 hours and duration of action of 12 to 36 hours [24]. Consequently, peripheral blood samples were obtained before surgery and after three days, when methylprednisolone's duration of action of was ended and haematological parameters were anticipated to be normalized.

Synthetic corticosteroids are widely used for management of inflammatory and immunologic conditions, such as allergies, rashes, asthma or arthritis [17,25,26]. Adrenal suppression, cardiovascular disease, Cushing's syndrome, dyslipidaemia, hyperglycaemia, immunosuppression and osteoporosis are well-known side effects associated with long-term corticosteroid therapy [27]. Local or systemic administration of a single dosage of corticosteroid is often used to diminish the inflammatory response following surgical removal of M3 [10]. However, adrenal suppression or severe side effects related to a single dosage of corticosteroid have never previously been described following surgical removal of M3 [10,11,28].

Systemic or local administration of synthetic corticosteroid interacts with haematological and biochemical parameters. Levels of haemoglobin and leucocytes in peripheral blood are usually increased following corticosteroid therapy [16,18]. In the present study, no statistical significant difference was observed in the level of haematological parameters between different dosages of methylprednisolone compared with placebo. However, the mean level of CRP was significantly decreased with 30 mg methylprednisolone compared with placebo indication a lower inflammatory reaction. Levels of CRP are influenced by various confounding factors including postoperative infection, time of surgery, body mass index, lack of exercise and medical conditions [29,30]. Moreover, anti-inflammatory drugs may cause a decrease in CRP levels. In the present study, subgroup analyses revealed equal distribution of postoperative infections and time of surgery among the four groups. Association between body mass index and daily physical functioning were not correlated to

levels of CRP and registration of quantity as well as time period of need for painkillers was not performed. The reported significant difference in CRP after administration of 30 mg methylprednisolone may therefore be related to another cause. Consequently, a single dosage of methylprednisolone seems not to significantly influence haematological parameters following surgical removal of M3.

Haematological parameters are influenced by various factors, including age, gender, ethnicity, diet, life-style, medication, anaemia, pregnancy, smoking and bleeding [25,26]. Therefore, patients with medical conditions, pregnancy or medical prescription influencing haematological parameters were excluded from the present study. Furthermore, results of peripheral blood samples were adjusted for age, gender, smoking and time of surgery.

Elderly patients are characterized by decreased level of haemoglobin and leucocytes in peripheral blood [24,26,31]. In the present study, there were no significant differences in the level of haemoglobin and leucocytes, when the results were correlated for age. However, patients' age ranged between 18 and 39 years, which might explain the reason for no statistical difference in the haematological parameters. However, pre- and postoperative peripheral blood samples revealed a significantly larger decreased in the level of eosinophils with increasing age. This result is in accordance with the literature demonstrating that levels of eosinophils decrease with advancing age [32].

Normal range of haemoglobin differs between genders and males generally have higher haemoglobin values than females [24,33]. In the present study, no statistically significant difference in the level of haemoglobin was observed between genders after administration of methylprednisolone compared with placebo. Thus, gender seems not to influence haematological parameters following surgical removal of M3 with a single intramuscular injection of methylprednisolone compared with placebo.

Smoking increases the level of haemoglobin, leucocytes and CRP in peripheral blood compared with non-smoking [34,35]. In the present study, there was no significant difference in level of leucocytes between smokers and non-smokers. However, a significant lower level of haemoglobin and CRP was observed in smokers compared with non-smokers. These results seems not to be in accordance with previous studies [34,35]. But only, five low smokers were included in the present study. Thus, the influence of smoking on haematological parameters within this study may not be representative.

Prolonged time of surgery may cause a decrease in the level of haemoglobin due to increased blood loss [36]. Surgical removal of M3 is usually associated with minor blood loss, though life-threatening haemorrhage has been reported [37]. Decreased level of haemoglobin following surgical removal of M3 is therefore not anticipated due to the insignificant blood loss. However, mean level of haemoglobin decreased in all groups, although blood loss were diminutive in all patients and no statistically significant difference in the level of haemoglobin was observed when the time of surgery was increased. Postoperative bleeding was observed in two patients, which did not affect the level of haemoglobin. Furthermore, level of leucocytes or CRP was not influenced by the time of surgery.

The present study is characterized by following limitations including small sample size, inclusion of smokers and non-smokers, dissimilar gender distribution and blood samples at different times with no regard to fast, sleep and physiological activities. Moreover, the life span of erythrocytes is approximately 90 days. Bone marrow suppression or disturbed erythropoiesis caused by a single dose of corticosteroids would therefore not be detectable in blood samples after solely three days. Assessment of long-term haematological parameters is therefore needed in further studies. Consequently, conclusions drawn from the present study should be interpreted with caution.

CONCLUSIONS

In conclusion, a single, intramuscular injection of methylprednisolone seems not to influence the short-term haematological parameters compared with placebo following surgical removal of mandibular third molars. However, further randomized controlled trials including larger patient samples, homogenous study groups and comparison of different synthetic corticosteroids are needed before definite conclusions can be provided about the influence of synthetic corticosteroids on haematological parameters following surgical removal of mandibular third molars.

ACKNOWLEDGMENTS AND DISCLOSURE STATEMENTS

A special thanks to MSc Lærke Brygger Madsen, Department of GCP at Aarhus and Aalborg University Hospital for assistance with the monitoring process, secretary Ms. Louise Fibiger Vangdal, Department of Oral and Maxillofacial Surgery, Aalborg University Hospital for efficient patient scheduling and MSc Rikke Nørmark Mortensen, Clinical Unit

of Biostatistics, Aalborg University Hospital for statistical analyses. Furthermore, a special thanks to MSc Kirsten Lykke Vorbeck, Pharmacy, Aalborg University Hospital for assistance with randomization procedure and production of medicine.
The study protocol was approved by the Danish Health and Medicines Authority (approval number: 56872, EudraCT-number: 2017-000622-35), Research Ethics Committee (approval number: N-20170016) and the Danish Data Protection Agency.
Patient consent: written informed consent was obtained from all included patients.
The authors report no conflicts of interest related to this study, as well as no funding to declare.

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To cite this article:
Larsen MK, Kofod T, Kirsten D, Starch-Jensen T.
Short-term Haematological Parameters Following Surgical Removal of Mandibular Third Molars with Different Doses of Methylprednisolone Compared with Placebo. A Randomized Controlled Trial
J Oral Maxillofac Res 2020;11(2):e3
URL: http://www.ejomr.org/JOMR/archives/2020/2/e3/v11n2e3.pdf
doi: 10.5037/jomr.2020.11203